Amendments to the Drawings:

The attached replacement sheets provide formal drawings of Figures 1-7 and replace the original sheets including Figures 1-7.

Attachments provided with this Amendment:

Transmittal of Formal Drawings and Replacement Sheets (5 pages)

REMARKS

Claims 1, 2, 6, 8-12, 14, 17, 19, 21-27, 32-36, 38-45, 83, 84, 86, 87, 89, 94-98 are pending in this application. Applicants have amended claims 1, 2, 6, 14, 17, 19, 33, 38-41, 45, 83, and 84, and canceled claims 28 and 90-93 without prejudice or disclaimer. Claims 94-98 are new. Support for the amendments can be found in the application, for example, at page 5, line 28 to page 6, line 2; page 7, lines 5-10; page 57, lines 3-5 and 14-19; page 58, lines 7-8; page 59, lines 18-23; page 60, lines 4-6; and page 69, lines 9-11.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the rejections of claims 1, 2, 6, 8-12, 14, 17, 19, 21-28, 32-36, 38-45, 83, 94, 86, 87, and 89-93 under 35 U.S.C. § 103.

Declaration

The Office Action correctly recognizes that the Declaration filed with the Reply of April 13, 2006 demonstrates the unexpected results obtained by using the a signal peptide from the pre-region and the pro-region of somatostatin to direct secretion of GLP-1.

However, the Office Action goes on to incorrectly mischaracterize the relevance of the cell type used for secretion of the small peptide. According to the Office Action at page 3:

> These results indicate that it is completely unpredictable whether a specific prepro-region of a secretory peptide would be able to direct peptide secretion in **a specific type of cells** [sic]. As such, **each specific construct and cell type** used for peptide secretion should be evaluated on its own merit based on evidence. Although the combined teachings of the cited art teach that the prepro-region of the somatostatin is useful in directing heterologous peptide secretion, none of them tested **the specific combination of the construct and cells** of the instant invention, i.e., the construct comprising a sequence encoding the prepro-region of a somatostatin and a sequence encoding a GLP-1, and **the foreskin fibroblast cells**. (emphasis added)

Applicants respectfully disagree with this allegation. The Declaration does not draw a distinction among non-endocrine cell types. For example, as stated at page 2 of the Declaration:

"Thus, based upon teachings such as Warren et al., it would be expected that even if GLP-1 was secreted by **non-endocrine cells** when associated with the prepro-region of somatostatin, it would be at fairly low levels," "Experiments were conducted to try to obtain secretion of GLP-1 from **non-endocrine cells** using various combinations of pre and/or pro regions ..." (emphasis added).

Indeed, in the Declaration, Dr. Concino states that the choice of signal peptide and pro-region are the factors that determine whether secretion of a small peptide can be obtained, "In my opinion, it is not clear why only the somatostastin prepro region, and none of the other pre and/or pro regions tested (including GLP-1's own naturally occurring pre pro region), could guide GLP-1 through the secretory pathway" (Declaration page 2-3). Dr. Concino makes absolutely no statement regarding the importance of the choice of cell type.

Likewise, Applicants' Reply of April 13, 2006 does not draw a distinction among non-endocrine cells types. For example, as stated in the previous Reply, "Applicants' discovery that GLP-1 can be secreted from **non-endocrine cells** using the prepro-region of somatostatin at significant levels was unexpected and surprising," (page 15) and

> Based upon the knowledge in the art that the prepro-region of somatostatin results in low levels of secretion of somatostatin from **non-endocrine cells** and the findings that the prepro regions naturally associated with GLP-1 result in no detectable GLP-1 secretion from **non-endocrine** cells, it was surprising to find that GLP-1 is expressed at statistically significant levels from **non-endocrine cells** when it is associated with the prepro-region of somatostatin." (page 15-16) (emphasis added)

Thus, as these examples demonstrate, Applicants have not drawn a distinction among non-endocrine cell types that can be used in practicing the subject matter recited in the claims. Rather, the Applicants have demonstrated that the choice of signal peptide and pro-region are instrumental in effecting secretion of a small peptide such as GLP-1 and variants thereof. As a result, Applicants submit that there is no basis for the Office Action's mischaracterization of the Declaration.

Formal Matters

Drawings

The Office Action states that the application lacks formal drawings. Applicants submit herewith five replacement pages containing formal drawings of Figures 1-7 of the application. No new matter has been introduced.

Specification

The Office Action has objected to the specification because in several passages, the specification recites "but no more than 5, 10, 12, 12, 25 ..." As indicated in the amendments to the specification of this reply, Applicants have amended the specification to correct this typographical error. The amendments to the specification do not introduce new matter.

35 U.S.C. § 112, First Paragraph, Enablement

The Office Action alleges that claims 1, 2, 6, 8-12, 14, 17, 19, 21-28, 32-36, 38-45, 83, 94, 86, 87, and 89-93 lack enablement. Specifically, the Office Action takes issue with the terms "a signal peptide," "a functional fragment," "a variant," "a GLP-1 analog," and "non-endocrine cell." Applicants respectfully disagree because these rejected claims, even prior to the amendments presented herein, can be practiced by the skilled artisan without undue experimentation.

With respect to the term "a signal peptide," the Office Action at page 5 states, "'a signal peptide' reads on any or all signal peptide." In the interest of expediting prosecution, Applicants have amended claims 1, 14, and 84 to recite that the signal peptide is from the pre-region of somatostatin. The somatostatin pre-region from various species, and signal sequences contained therein, are described in the application (e.g., page 58, lines 7-15; and original claims 2, 28, 54, and 83). Page 58, lines 16-23 describes how to optimize nucleic acid sequences encoding signal sequences. Further, the application describes how to test a candidate signal sequence for suitability in the disclosed invention. For example, page 58, line 24 to page 59, line 2 describes an *in vitro* assay that can be used to test a signal peptide. Thus, Applicants submit that a skilled artisan could prepare a construct of the invention that contains a signal peptide from the pre-

region of somatostatin without undue experimentation, but rather by exercising routine experimentation.

Next, the Office Action alleges at page 5 that "the variant of the pro-region of a somatostatin reads on a variant with less than 80% sequence homology to the referenced sequence (as there are 64 amino acids for the pro-region of the somatostatin)," and further states, at page 5-6, "the specification does not disclose or test any functional fragment or variant of the pro-region of a somatostatin, which would meet limitation of the claims, nor guidance or working example regarding same." Applicants respectfully disagree because the application provides ample guidance in the selection and testing of functional fragments and variants of the somatostain pro-region.

Page 59, lines 13-17 indicate that nucleotide sequence information on pro-somatostatin from various species is known in the art; page 59, lines 18-26 describe how to optimize functional fragments and variants of the pro-region; and page 59, line 27 to page 60, line 6 describe preferred variants, e.g., that contain conservative amino acid substitutions and that vary by a fixed number of differences from the wild type sequence. Page 59, lines 7-11 describe how to make variants. Next, page 59, lines 12-17 describe how to test fragments and variants for suitability for use in the claimed subject matter. In addition, Applicants have amended claims 1 and 14 to recite that "the functional fragment or variant differs from the wild-type amino acid sequence by at least 1 but not more than 5 amino acid residues and is sufficient to promote secretion from a cell." As a result of this amendment, the claims do not "read[] on a variant with less than 80% sequence homology to the referenced sequence." Instead, these claims recite sequences that are over 92% identical to the sequence of the wild-type somatostain pro-region, and that retain a function of the wild-type sequence. Thus, using ordinary skill and routine experimentation, a skilled practitioner could easily make and test functional fragments and variants of the somatostatin pro-region recited in the claims. Finally, several claims recite the use of the pro-somatostatin region without variation (see, e.g., claims 83, 84, 89, 94, 98).

Regarding the analog of GLP-1, the Office Action at page 6 states,

> With respect to an "analog" of GLP-1, the specification does not define the term, thus, given the broadest and reasonable interpretation, it reads on a functional equivalent with or without sequence homology to GLP-1. With the exception of

> several GLP-1 sequence variants (GLP-1 (7-37), (GLP-1 (7-36), and GLP-1-Gly8 (page 12, the second paragraph, for example), no other functional equivalents meeting the limitations of the claims were ever identified or particularly described in the specification. The specification fails to provide guidance or working examples of any functional equivalent of GLP-1, which may not share sequence homology, and would be within the limitations of the claims. Therefore, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

Applicants disagree with this assertion, but in the interest of expediting allowance of this case, have amended claims 1, 14, 38, and 41 to replace the term "analog" with the term "variant." The application is replete with examples of variants of GLP-1, and provides working examples that demonstrate the preparation of GLP-1 variants. The examples further demonstrate secretion of a variant when a nucleic acid construct containing sequences encoding a signal peptide from the pre-region of somatostatin, the pro-region of somatostatin, and a GLP-1 variant are expressed in non-endocrine cells. For example, page 2, lines 10-14; page 57, lines 3-6 and lines 14-19; page 69, lines 9-11; page 72, lines 16-25; and Figure 4 provide examples of numerous specific GLP-1 variants. These variants include: GLP-1 (7-34), GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-37), Gln^{9}-GLP-1 (7-37), Thr^{16}- Lys^{18}-GLP-1 (7-37), Lys^{18}-GLP-1 (7-37), Gly^{8}-GLP-1, Met^{16}-Met^{20}-GLP-1 (7-37). Page 57, lines 6-14 describes how to optimize variants for expression. Examples I through V on pages 68-74 provide examples on how to make and use various GLP-1 variants. Thus, Applicants submit that the present application more than sufficiently enable the pending claims with respect to the term "GLP-1 variants."

> Finally, the Office Action objects to the term "non-endocrine cell," alleging at page 6 that the term "non-endocrine cell" encompass any or all type of non-endocrine cells. However, only human foreskin fibroblast cells are tested and used for making GLP-1 peptide in the instant specification. **Given the result disclosed in the declaration** that GLP-1's own naturally occurring pre pro region does not result in GLP-1 secretion from the fibroblasts used, **it strongly indicates that the cell type is critical for peptide secretion** as GLP-1 is secreted from its naturally occurring endocrine cells. Once again, **as indicated by applicants in the declaration,** that it is not clear why only the somatostatin prepro region, and none of the others tested, including GLP-1 's own naturally occurring pre pro region, could guide GLP-1 through the secretory pathway (in the foreskin fibroblast cells). Therefore, it is completely unpredictable which type of non-endocrine cells

> would be suitable for the claimed construct to make secreted GLP-1, and it would require undue experimentation to identify other non-endocrine cells having the desired property, and determine if such were suited to be used as claimed. (emphasis added)

Applicant disagree. First, as discussed above, the Office Action is mischaracterizing the Declaration filed with Applicants' previous Reply. The Declaration does not state or suggest that the specific type of non-endocrine cell matters, nor does it state or suggest that the specific cell type is "critical" for secretion. Rather, the Declaration describes how the choice of signal peptide (from the pre-region of somatostatin) and pro-region are important. As stated in the Declaration (and mis-quoted in the passage from the Office Action), "In my opinion, it is not clear why only the **somatostastin prepro region**, and none of the other pre and/or pro regions tested (including GLP-1's own naturally occurring pre pro region), could guide GLP-1 through the secretory pathway" (pages 2-3; emphasis added). The Declaration makes absolutely no mention of the criticality of a particular non-endocrine cell type, not to mention the criticality of fibroblasts.

The claims have been amended to recite "non-endocrine" cells. Applicants submit that claims reciting this term, and the claims that depend therefrom, are enabled by the present application, and can be practiced without undue experimentation. Specifically, the application provides examples demonstrating the use of a non-endocrine cell type (see Examples II through V on pages 70-74) and provides guidance on how to make and use cells that express and secrete GLP-1 or variants thereof. For example, page 61, line 5 to page 62, line 19 describes how to genetically engineer cells. Specifically, examples of cells that can be used and how to introduce exogenous nucleic acid sequences into cells are provided. Page 62, line 21 to page 64, line 12 describes how to transfect cells. Page 67, line 9 to page 68, line 3 describes how to use the transfected cells. Further, the application provides examples of various cell types that can be used in practicing the subject matter recited in the claims (see, e.g., page 5, line 28 to page 6, line 18). The suitability of these cell types to effect expression and secretion of GLP-1 or a variant thereof can easily be tested using an assay described in the Examples of the application, e.g., cells can be transfected with a nucleic acid construct of the application and the media of the cell

culture can be tested for secretion of GLP-1 or a variant thereof. For example, as demonstrated in Example II (page 71), such transfections and assays of culture media (e.g., by Western blotting) are routine in the art and can be practiced using ordinary skill and without undue experimentation. Applicants submit that claims reciting the term "non-endocrine cells" are enabled.

To conclude, Applicants respectfully submit that the pending claims are enabled and can be practiced without undue experimentation. Applicants request that the enablement rejection of claims 1, 2, 6, 8-12, 14, 17, 19, 21-27, 32-36, 38-45, 83, 94, 86, 87, and 89 be withdrawn (claims 28 and 90-93 have been canceled).

CONCLUSION

Applicants respectfully submit that all claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above.

Enclosed is a $120 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10278-014001.

Respectfully submitted,

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